CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205777Orig1s000

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

Date	July 23, 2014
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	205777
Applicant Name	Purdue Pharma, L.P.
Date of Submission	September 23, 2013
PDUFA Goal Date	July 23, 2014
Proprietary Name / Established (USAN) Name	Targiniq ER Oxycodone HCl and naloxone HCl extended-release tablets
Dosage Forms / Strength	10/5 mg, 20/10 mg, 40/20 mg tablets
Proposed Indication	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Ellen Fields, M.D., M.P.H.
Clinical Review	Elizabeth Kilgore, M.D.
Biostatistics Review	Feng Li, Ph.D.; Janice Derr, Ph.D. (DBII); Janelle Charles, Ph.D.; Mat Soukup, Ph.D.; Aloka Chakravarty, Ph.D. (DBVII); Ling Chen, Ph.D.; Anna Sun, Ph.D.; Yi Tsong, Ph.D. (CSS/DBVI); Mohammed Rahman, Ph.D.; Karl Lin, Ph.D. (carcinogenicity/DBVI)
Pharmacology Toxicology Review	BeLinda Hayes, Ph.D.; R. Daniel Mellon, Ph.D.
ONDQA-CMC/Quality Review	Eugenia Nashed, Ph.D.; Julia Pinto, Ph.D.
Microbiology	Steven Donald, MS; Steven Langulle, Ph.D.
Biopharmaceutics Review	Kareen Riviere, Ph.D.; Tapash Ghosh, Ph.D.
Clinical Pharmacology Review	Srikanth Nallani, Ph.D.; Yun Xu, Ph.D.
OSI	Cynthia Kleppinger, M.D.; Janice K. Pohlman, M.D., M.P.H.; Kassa Ayalew, M.D., M.P.H.
Project Management	Lisa E. Basham, M.S.; Parinda Jani; Luz Rivera (CMC)
Controlled Substance Staff	James Tolliver, Ph.D.; Silvia Calderon, Ph.D.; Muichael Klein, Ph.D.
OSE/DMEPA	Vicky Borders-Hemphill, Pharm.D.; Morgan Walker, Pharm.D.; Irene Chan, Pharm.D..
OSE/DRISK	Kimberly Lehrfeld, Pharm.D.; Reema Mehta, Pharm.D., M.P.H.
OMP/OMPI/DMPP	Karen Dowdy, R.N., B.S.N.; Barbara Fuller, R.N., M.S.N., C.W.O.C.N.; LaShawn Griffiths, M.S.H.S-P.H., B.S.N.; R.N.
OMP/OPDP	Eunice Chung-Davies, Pharm.D.
Controlled Substances Staff	James Tolliver, Ph.D.; Silvia Calderon, Ph.D.; Michael Klein, Ph.D.
PMHS	Miriam Dinatale, D.O.; Jeanine Best, M.S.N., R.N., P.N.P.; Lynne Yao, M.D.
DCRP	Preston Dunmon, M.D.; Norman Stockbridge, M.D., Ph.D.

OND=Office of New Drugs
OMP: Office of Medical Policy
OMPI=Office of Medical Policy Initiative
OSE= Office of Surveillance and Epidemiology
OPE=Office of Pharmacovigilance and Epidemiology
DMEPA=Division of Medication Error Prevention
DRISK= Division of Riak Management
DCRP=Division Cardio-Renal Products
OPDP= Office of Prescription Drug Promotion
DMPP = Division of Medical Policy Programs
OSI=Office of Scientific Investigations
CDTL=Cross Discipline Team Leader
ONDQA=Office of New Drug Quality Assessment
CMC=Chemistry, Manufacturing, and Controls
PMHS =Pediatric and Maternal Health Staff

1. Introduction

Purdue Pharma, L.P. submitted this application for Targiniq ER, oxycodone HCl/naloxone HCl extended-release tablets, as a fixed-dose combination drug product with an indication consistent with the class indication for ER/LA opioids, for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." The NDA was submitted as a 505(b)(2) referencing Narcan, NDA 016636, as the listed drug, and cross referencing Purdue's own NDAs for OxyContin and reformulated OxyContin. The Applicant has submitted studies to support that Targiniq ER's formulation provides abuse-deterrent features for the intravenous and intranasal routes of abuse. Although the Applicant requested a priority review, they did not perform head-to-head comparison studies with their already approved OxyContin to demonstrate an overall improvement in abuse-deterrent qualities. Therefore, considering the existence of an approved, extended-release oxycodone product on the market, and an absence of evidence to support the superiority of this product, the application was reviewed on a standard clock. Overall, the review team found that the application provided sufficient support to establish the safety and efficacy of Targiniq ER and they have recommended approval of the NDA.

2. Background

This product was developed to provide both abuse deterrence (b) (4) based on the inclusion of naloxone in the formulation. It is marketed outside the US with an indication for the management of OIC under the trade name Targin. During development in the US, the Applicant decided to submit their NDA initially for the analgesia indication and include data to support the inclusion of some abuse-deterrent features into the product labeling (b) (4) However, it is important to note that there has been some concern raised recently regarding products (b) (4) and a possible increased risk of cardiovascular toxicity. The very mu-opioid antagonist activity of the naloxone that appears to provide some abuse-deterrence to the product acting centrally, also results in apparent antagonism of peripheral receptors which may be associated with signs and symptoms of withdrawal. This topic was presented at a meeting of the Anesthetics and Analgesics Products Advisory Committee (AADPAC) recently and, based on the results of that meeting, an additional postmarketing safety study is being required of products in this class. Additional discussion regarding this safety concern is included below in Section 9. Of note, there is an upper dose limit for Targiniq ER, unlike OxyContin, due to the tolerability of the naloxone component. At

doses higher than 80/40 mg adverse events, including many that appeared to be due to opioid withdrawal, increased to a level resulting in an unacceptable benefit-risk balance.

3. CMC

The following summary of the Chemistry, Manufacturing and Controls data, and the Biopharmaceutics and Microbiology data, submitted in the application has been reproduced from pages 4 and 5 of Dr. Fields' review:

> There are two drug substances in TARGINIC ER, oxycodone hydrochloride and naloxone hydrochloride. The oxycodone drug substance is supported by DMF (b) (4) which has as adequate status. The naloxone hydrochloride drug substance is supported by DMF (b) (4) which has an adequate status, and DMF (b) (4) which has an inadequate status, based on review by the Office of Generic Drugs (OGD) completed June 3, 2014. The deficiency in DMF (b) (4) is regarding the modification (b) (4) In her review, Dr. Nashed recommended not approving TARGINIC ER based on the issue with the (b) (4) DMF. However, following additional discussion, Dr. Pinto entered a review into DARRTS on June 26, 2014 stating the following:
>
> > Under GDUFA, the (OGD) reviewer recommended the processes be split into two DMFs. Therefore, since the deficiency is not safety or quality related, and since sufficient data is provided within the NDA to support the naloxone drug substance obtained (b) (4) under this DMF, NDA 205777 is recommended for approval from the CMC perspective.
>
> Several information requests were sent to the Applicant to tighten the acceptance specifications to the ICH Q3A-recommended levels for drug substance impurities, (b) (4) Dr. Nasheed wrote that while the proposed acceptance criteria may be adequate for a maximum daily dose (MDD) of TARGINIC ER 80/40 mg, it is not adequate for higher MDDs. At the time of completion of Dr. Nasheed's review, the MDD had not been confirmed by the Division. However, since then the maximum daily dose has been designated as 80/40 mg (see NonClinical and Clinical Pharmacology sections of this review), and therefore, the Applicant has provided sufficient data to support the acceptance criteria.
>
> Dr. Nasheed describes the drug product manufacturing as follows:
>
> (b) (4)

(b) (4)

The proposed expiry of 24 months is acceptable based on the maximum recommended dose of 80/40 mg.

The EER recommendation from the Office of Compliance is Acceptable.

Microbiology safety controls were found adequate per review by Steven Donald, Ph.D., microbiology reviewer.

I concur with the review team that there are no outstanding CMC concerns that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The following summary of the nonclinical pharmacology and toxicology data submitted in this application has been reproduced from pages 10 through 12 of Dr. Hayes' review:

To support the safety of the drug product, the Applicant submitted the full standard battery of nonclinical toxicology studies for naloxone and resubmitted the oxycodone toxicology studies previously completed to support the OxyContin program. In addition, the Applicant submitted 3-month general toxicology studies evaluating the combination of oxycodone and naloxone.

The relative safety of oxycodone alone has been established in the development programs for OxyContin and via post-marketing experience. Characterization of the toxicologic potential of naloxone at the proposed doses and duration required additional studies to support this program. Although the general toxicology studies suggested that high doses of naloxone can produce convulsions in animals, there is an adequate safety margin (>60-fold) for the proposed maximum recommended daily dose of naloxone via this drug product.

The standard ICH battery of genetic toxicology studies were conducted for oxycodone HCl and naloxone HCl. Genetic toxicology studies submitted for oxycodone HCl was previously submitted to support the NDAs for Oxycontin. Oxycodone tested negative in the in vitro bacterial reverse mutation assay for mutagenicity and the in vivo bone marrow micronucleus assay. However, oxycodone was positive in the in vitro chromosomal aberration assay for mutagenicity in the presence of metabolic activation. Likewise, naloxone tested negative in the in vitro bacterial reverse mutation assay and the in vivo mouse micronucleus assay. However, naloxone also tested positive in the L5178Y mouse lymphoma assay.

No reproductive studies and developmental studies were conducted using the oxycodone and naloxone combination. However, reproductive toxicology studies were performed with naloxone hydrochloride (b) (4) Embryo-fetal developmental studies conducted in pregnant rats treated with 50, 200, and 800 mg/kg/day naloxone hydrochloride by oral gavage during organogenesis. No remarkable treatment-related maternal toxicity was observed at doses up to 800 mg/kg/day. The maternal NOAEL

was established at 800 mg/kg/day (192-fold human systemic exposure based on a mg/m2 comparison. No developmental toxicity was observed at doses up to 800 mg/kg/day; the NOAEL for developmental toxicity was established at 800 mg/kg/day (192-fold human systemic exposure based on mg/m2).

Embryo-fetal developmental studies were conducted in New Zealand White rabbits treated with 20, 100, or 400 mg/kg/day naloxone hydrochloride by oral gavage during organogenesis. Naloxone was not teratogenic under the conditions of the assay; no significant malformations (external, soft tissue, or skeletal) were noted at doses up to 400 mg/kg/day. The maternal NOAEL was established at 100 mg/kg/day based on a non-statistical decrease in implantation rate, mean number of females per litter, and number of live fetus per dams. The developmental NOAEL is established at > 400 mg/kg/day based on lack of developmental toxicity (192-times the maximum recommended daily dose of 40 mg naloxone, on a body surface area basis).

Pre- and post-natal studies were conducted in pregnant rats treated with 50, 200, and 800 mg/kg/day naloxone hydrochloride by oral gavage from organogenesis through weaning. Evidence of maternal toxicity was indicated by treatment-related mortalities at the 800 mg/kg/day level and decreased body weight gain at the 200 mg/kg/day. The maternal NOAEL was established at 50 mg/kg/day (estimated exposure approximately 192-fold on a mg/m2 basis). The developmental NOAEL was established at 200 mg/kg/day based on reduced viability index and newborns per litter from dams orally administered 800 mg/kg/day naloxone.

Collectively, although the existing oxycodone reproductive and developmental toxicology data do not suggest concern for the maximum recommended daily dose of oxycodone via this formulation, and there is an adequate safety margin for any naloxone-mediated effects, there appears to be little reproductive and developmental toxicology risk with this product. However, as there are not studies with the combination, we recommend that the drug product be given a Pregnancy Category C.

No carcinogenicity studies were conducted using the oxycodone and naloxone combination. However, carcinogenicity studies were performed with naloxone hydrochloride. Naloxone was negative in a 26-week Tg rasH2 mouse carcinogenicity study and in a 2-year dietary rat carcinogenicity study at doses of 4, 20, or 100 mg/kg/day naloxone HCl showed no evidence of treatment-related tumors (24-times the human dose of 40 mg/day on a mg/m2 basis). Carcinogenicity data on oxycodone do not exist and based on OND policy, these studies will not be required for this drug product since the exposures to oxycodone via this formulation do not result in novel exposures compared to the cross-referenced OxyContin drug product.

Adequate safety data for the excipients in the drug has been provided for the maximum recommended daily dose of up to 80 mg oxycodone and 40 mg naloxone vis this drug product. The proposed drug substance and drug product specifications are acceptable for approval at this time. The drug substance impurity (b) (4) which contains a structural alert for mutagenicity, has historically been limited to not more than (NMT) (b) (4) for existing drug product formulations largey based on the relatively low daily exposures to naloxone. However, this drug product results in greater exposure to naloxone, therefore, the Applicant was asked to reduce the level to NMT (b) (4) This would require a specification of NMT (b) (4). To date, the drug substance manufacturers are able to reach (b) (4) for this impurity, but are not able to reduce it further at this time. Therefore, although not an approval issue, since this is as low as technically feasible, a PMR should be issued to either reduce the

levels to NMT [redacted] (b) (4) or to adequately qualify the impurity for safety. This would require an in vivo micronucleus assay and an in vivo comet assay testing both stomach and liver tissue.

It should be noted that this maximum recommended daily dose (MRDD) is not acceptable for single entity controlled relese oxycodone drug products, which are taken at much higher levels due to the development of tolerance. This MRDD is based on the presence of the naloxone in the drug product, which is believed to limit the drug product's utility at higher doses. However, should the drug product be deemed appropriate for dosing above the MRDD of 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride, further safety justification for the levels of excipients, drug substance impurities, and drug product degradants will be required.

I concur with the review team that there are no outstanding nonclinical pharmacology or toxicology concerns that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology and biopharmaceutics has been reproduced from pages 8 through 12 of Dr. Fields' review:

As summarized by Dr. Nallani in his review:

For this 505(b)(2) NDA, Purdue has conducted the relative bioavailability study ONU1009, which established a pharmacokinetic (PK) bridge of each component of Tradename (oxycodone and naloxone) to approved NDA products, OxyContin (oxycodone extended release NDA 022272 and its predecessor NDA 020553) and Narcan (Naloxone, NDA 016-636, via an ANDA generic designated as the Reference Listed Drug for Narcan since Narcan is not available on the market).

A total of 23 Phase 1 clinical studies and 1 Phase 2 clinical study were conducted as part of the Tradename clinical pharmacology program to support the Tradename dosage regimen proposed for US registration. These studies characterized the PK and PD properties, effect of age, sex, special populations, drug interaction potential, abuse deterrence, and GI motility effects associated with Tradename. The results of these studies support the proposed BID dosing regimen and dosage range, within which the exposures to oxycodone from Tradename are bioequivalent to those from the oxycodone CR marketed products including reformulated OxyContin and Oxygesic, the European marketed product. Eighteen of the clinical studies were reviewed. The main goal of the clinical pharmacology review is to focus on the clinical and clinical pharmacology studies with regard to impact of naloxone on clinical safety and efficacy.

Oxycodone Pharmacokinetics

Purdue Pharma conducted a randomized crossover study (ONU1009) in healthy volunteers (n=27) to assess the relative bioavailability of Tradename (Oral Oxycodone 20 mg and Naloxone 10 mg) as compared to IV naloxone 0.4 mg and oral OxyContin 20 mg. Oxycodone Cmax and AUC were bioequivalent between Tradename and Oxycontin. In a separate

study (OXN1506) pharmacokinetics of oxycodone were observed to be dose-proportional for Tradename strengths proposed 10/5 mg, 20/10 mg and 40/20 mg. Food-effect study (OXN1003) revealed a 25% increase in Cmax and a 17% increase in AUC for oxycodone following administration of Tradename (40/20 mg) with high-fat meal compared to fasting. Following multiple dose administration (BID) systemic exposure of oxycodone was similar to that noted with a controlled release oxycodone (similar to OxyContin) on Day 4.

Naloxone Pharmacokinetics

Observations from the relative bioavailability study ONU1009 also provide a context for the plasma naloxone levels. Parenteral (IV, IM or SC) naloxone is commonly used in the treatment of reversing opioid overdose with a dose range from 0.4 mg to 2 mg based on Narcan label. Additionally, parenteral (0.2 to 0.6 mg IM or IV) naloxone challenge test is used to screen for subjects claiming to be recreational users of opioids. Absolute bioavailability of naloxone from Tradename was <1% as measured by dose-normalized AUC. The first noted plasma concentrations of naloxone (at 30 min) following IV administration were 1.26 ± 0.37 ng/mL (Range 0.725 to 2 ng/mL).

As mentioned before, (b) (4) because of low oral bioavailability plasma levels of naloxone are very low. Under normal circumstances, systemic levels of naloxone in majority of the subjects were observed to be low (<0.725 ng/mL, the lower end of the observed concentration at T= 30 min) and highly variable. Dose-proportionality in naloxone PK is **not** noted with increased doses of TARGINIC ER.

Administration of TARGINIC ER with food resulted in higher plasma levels of naloxone compared to fasted state. Four different food-effect studies were conducted where a worst case of 75% increase in plasma levels of naloxone was noted with TARGINIC ER 40/20 mg (Study OXN1003). This observed increase in plasma naloxone levels may not be clinically significant.

Of note, plasma levels of naloxone following administration of a single dose of 40/20 mg of TARGINIC ER in the fed state, are highly variable, with a range of concentrations between 0.05 ng/mL to 1.034 ng/mL.

Treatment	N	Mean (ng/mL)	SD	Median (ng/mL)	Min (ng/mL)	Max (ng/mL)
Study OXN 1003 (Food Effect Study)						
Targiniq 10/5 Fast	27	0.025	0.024	0.016	0	0.103
Targiniq 10/5 Fed	26	0.051	0.046	0.032	0.016	0.205
Targiniq 40/20 Fast	25	0.074	0.044	0.054	0.03	0.177
Targiniq 40/20 Fed	26	0.14	0.19	0.085	0.05	1.034

During the NDA review cycle, the nonclinical team required that the Applicant address the safety of excipients used in the TARGINIC ER formulation, which is typically done by determining the maximum theoretical daily dose (MTDD) a patient could take and using that to compare the levels of excipients to the inactive ingredient safety database. The Applicant has proposed a maximum daily dose of TARGINIC ER of 80/40 mg administered as 40/20 mg BID. They based this on clinical experience in Study ONU3701 where this was the highest dose studied, and postmarketing experience outside the US. The Applicant was asked to provide a justification for the proposed MTDD, and data to support why patients would not take more than 80/40 mg per day.

> *Based on the information provided to date, you have concluded that there are insufficient data to support dosing above 80 mg oxycodone/40 mg of naloxone per day via your drug product. However, you have not provided any data to support that TARGINIC ER should not be used at higher daily doses. We note that all currently approved single-entity oxycodone drug products have no maximum daily dose listed in the drug product labeling. Therefore in the absence of data to support the proposed dosing limit, we will use the maximum theoretical daily dose of 1.5 grams of oxycodone (750 mg of naloxone) per day that is applied to extended-release oxycodone products.*

The Applicant was not able to address this information request satisfactorily.

To assist in answering whether 80/40 mg is the appropriate MTDD for TARGINIC ER, Dr. Nallani performed pharmacokinetic simulations utilizing the naloxone Cmax as a limitation to the use of higher doses of TARGINIC ER. The relevant question here is what dose of TARGINIC ER would result in a naloxone exposure level high enough to block efficacy or trigger opioid withdrawal in a substantial number of patients when TARGINIC ER is taken as directed.

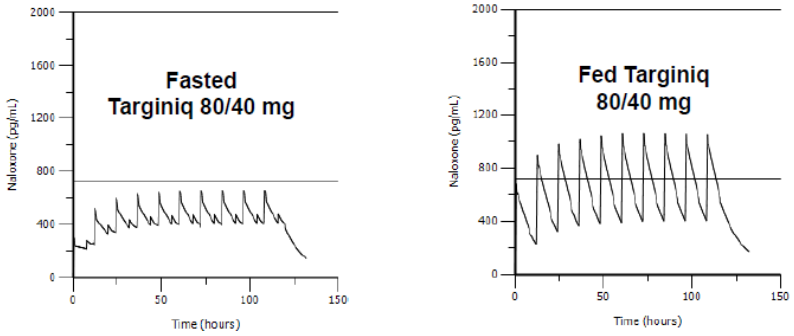
Dr. Nallani stated in his review:

> IM or IV injection of naloxone 0.4 mg is commonly used in the naloxone challenge test. Plasma naloxone concentrations were noted to be 1.26 ng/mL (range 0.725 – 2 ng/mL) at 30 minutes following IV bolus administration.

In the PK simulations, Dr. Nallani used a systemic naloxone concentration of 725 pg/ml as the lowest level at which opioid withdrawal may occur, based on the data from the single 0.4 mg dose of naloxone that is used to reverse opioid overdose symptoms. He noted the following:

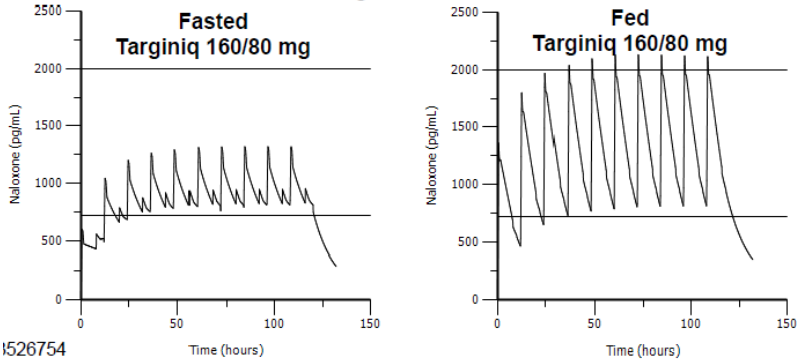
1. Simulated plasma naloxone levels for TARGINIC ER 80/40 mg BID (total daily dose 160/80 mg)

Figure: Simulated Naloxone PK Profile in fasted (left) and fed (right) condition following twice daily administration of Targiniq 80/40 mg strength with a total daily dose of 160/80 mg (based on data from OXN1505). Reference lines indicate the range of observed plasma concentrations at 30 minutes following IV bolus administration of IV naloxone.



2. Simulated plasma naloxone levels for TARGINIC ER 160/80 mg BID (total daily dose 320/160 mg)

Figure: Simulated Naloxone PK Profile in fasted (left) and fed (right) condition following twice daily administration of Targiniq 160/80 mg strength with a total daily dose of 320/160 mg (based on data from OXN1505 and assumed dose-proportional PK). Reference lines indicate the range of observed plasma concentrations at 30 minutes following IV bolus administration of IV naloxone.



The total daily dose of 160/80 mg results in naloxone plasma levels that are greater than 750 pg/ml for the fed state only, and for total daily dose of 320/160 mg, plasma levels are above 750 pg/ml for both fed and fasted. Referring back to the results of Study OXN1003 above, the Cmax levels for a single dose of TARGINIC ER 40/20 mg are very variable, with a mean of Cmax of 140 pg/ml in the fed state (below the 725ng/ml cutoff), and a maximum Cmax in the fed state is well above the 725 pg/ml level at 1034 pg/ml.

In Dr. Nallani's review, page 8, he states that:

> …simulated plasma naloxone levels that are more likely to produce opioid-blockade or opioid-withdrawal in dependent subjects may occur under following circumstances:
>
> - TARGINIQ ER 160/80 mg dose administered twice daily under fasted or fed condition
>
> (total daily dose of 320/160 mg) or,
>
> - TARGINIQ ER 80/40 mg dose administered under fed condition (high-fat meal consumption) twice daily (total daily dose of 160/80 mg under fed condition)

Based on the fact that TARGINIC ER may be administered without regard to food intake, the high intersubject variability in systemic exposure, and that the PK modeling showed that the 160/80 mg total daily dose taken with food results in a plasma level of naloxone higher than 750 pg/ml, the level at which opioid withdrawal may occur, I recommend that the maximum dose be designated as 80/40 mg (40/20 mg BID). Please refer to the nonclinical section of this review for additional information.

The following summary of the biopharmaceutics data submitted with this application has been reproduced from page 18 of Dr. Fields' review:

> …[*The*] review focused on the evaluation and acceptability of the proposed dissolution method, the proposed dissolution acceptance criteria, information and data on alcohol dose dumping, data supporting the bioequivalence of the proposed product manufactured in the US and Europe for each strength, and data supporting the in vitro in vivo relationship (IVIVR) for the oxycodone component of the proposed drug product.
>
> In summary, the dissolution method and proposed acceptance criteria are acceptable. The Applicant provided in vitro data demonstrating no potential for alcohol dose-dumping. Adequate data was provided to demonstrate the bioequivalence of the proposed product manufactured in the US and Europe. Thus clinical and clinical pharmacology data generated with the European product may be used to support approval of the US product. The Applicant attempted to establish a model with the relationship between in vitro tablet dissolution rates and in vivo absorption/bioavailability for the oxycodone component of the proposed product. However, the submitted report lacked detailed information on the assumptions and procedures taken to develop and validate this model. Therefore, it serves no regulatory purposes to implement any possible change that will affect oxycodone alone in this combination controlled release product.

I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application. Pharmacokinetic data related specifically to the abuse-deterrent features of the product were incorporated into the CSS review and are discussed below in Section 11.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

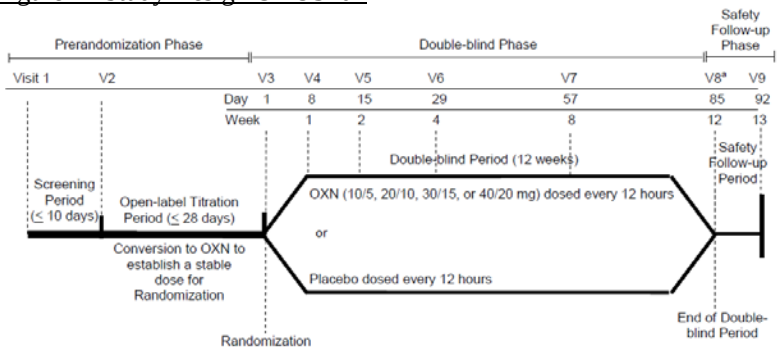
The following summary of the efficacy data for this application has been reproduced from pages 19 through 24 of Dr. Fields' review:

As a 505(b)(2) application, referencing the Listed Drug, Narcan, with cross-reference to the original OxyContin and reformulated OxyContin NDAs, the Division advised the Applicant that a clinical trial demonstrating efficacy would be needed if detectable levels of naloxone in systemic circulation were noted, and agreed with the Applicant that one positive adequate and well-controlled clinical trial was necessary to support a finding of efficacy for the proposed indication was sufficient. The Division also advised the Applicant that the primary efficacy endpoint must measure pain over a 12-week treatment period to support a chronic pain indication, and a landmark analysis was the preferred approach. Discussions were also conducted regarding the use of imputation methods to account for missing data.

Study Design ONU3701

Study ONU3701, conducted in opioid-experienced subjects with chronic low back pain, was submitted to support the efficacy of OXN administered twice daily compared to placebo. It was a double-blind, placebo-controlled, parallel group, randomized withdrawal study of OXN in subjects with moderate-to-severe chronic low back pain. The study consisted of three phases: the pre-randomization phase including a screening period and an open-label titration period (up to 28 days), the 12-week double-blind phase, and the safety follow-up phase. Subjects who demonstrated analgesic benefit and acceptable tolerability with OXN treatment during the open-label titration period were eligible for entering the double-blind phase.

Figure X Study Design ONU3701



Source: Applicant's CSR3701, p. 23

In order for subjects to enter the open-label titration period, they must have had an average pain over the prior 24 hours of at least 5 on an 11-point NRS, and a total average daily opioid dose over the screening period of 20 to 160 mg morphine equivalents of an opioid analgesic, or tramadol with dose of at least 100 mg daily. At entry into the open-label titration, all subjects were converted from their current opioid to OXN at an oxycodone dose approximately equivalent to their current therapy. A conversion table was supplied to the investigators, however, they were allowed to use their own discretion regarding the dose of OXN selected. OXN doses could be adjusted up or down based on effectiveness and tolerability, the maximum allowed

dose being OXN 40/20 mg BID. Subjects entering the double-blind phase were required to have demonstrated analgesic benefit and acceptable tolerability with OXN treatment during the open-label titration period. Subjects were then randomized to receive either OXN or matching placebo every 12 hours, based on their OXN dose at the end of the open-label titration period. Supplemental pain medication (IR oxycodone) for breakthrough low back pain was allowed except during the 30 hours preceding study visits. The first 10 days of the double-blind period constituted a randomized withdrawal phase where subjects randomized to placebo were tapered off OXN in a blinded fashion. The double-blind phase comprised six visits: visit 3 (randomization), visit 4 (Week 1 ± 2 days), visit 5 (Week 2 ± 2 days), visit 6 (Week 4 ± 3 days), visit 7 (Week 8 ± 3 days), and visit 8 (Week12 ± 3 days). A seven-day follow up visit was conducted following completion of the double-blind phase or early discontinuation.

At scheduled study visits, efficacy assessments included "average pain over the last 24 hours" using an 11-point NRS, Brief Pain Inventory-Short Form (BPI-SF), the Clinical Opioid Withdrawal Scale (COWS), the modified Subjective Opioid Withdrawal Scale (SOWS), and Medical Outcomes Study (MOS) sleep scale.

The primary efficacy outcome was the "average pain over the last 24 hours" at Week 12. The secondary efficacy outcomes included Patient Global Impression of Chang (PGIC) and MOS
Sleep Disturbance Subscale score at Week 12. Safety assessments included collection of adverse events, Clinical Opioid Withdrawal Scale (COWS), modified Subject Opioid Withdrawal Scale (SOWS), clinical laboratory tests, vital signs and ECGs. Pharmacokinetic assessments were also conducted at Visit 3 and Visit 6, and clinic visits where the subject had a COWS score ≥13 or an adverse event of opioid withdrawal.

Results ONU3701
Study design and conduct were reviewed by Dr. Kilgore. The Applicant determined that 10% of subjects in both the OXN and placebo groups had major protocol violations that could have affected efficacy analyses. These subjects were excluded from the per protocol analyses. All subjects (n=17) from one study site (2214A-9015) were excluded from analysis due to allegations that the investigator was involved in writing prescriptions illegally for purposes of abuse. There did not appear to be protocol amendments or protocol deviations that would be expected to affect the efficacy results.

There were 1095 subjects who received open-label titration treatment, and 600 subjects who entered the double-blind phase of the study (placebo-302, OXN-298). During the open-label titration, 45% of subjects discontinued the study, approximately 9% due to adverse events, 10% due to lack of efficacy, and 16% did not qualify for entry into the double-blind phase. Of the 600 subjects entering the double-blind phase, 399 completed it, with the most common reason for early discontinuation being lack of therapeutic effect (17%), followed by adverse events (8%). Discontinuation due to lack of efficacy was more common in the placebo group (24%) compared to OXN (10%) as would be expected. Discontinuation due to adverse events was similar in both groups (10%). The Applicant's table below shows the disposition of patients in detail.

Table X: Subject Disposition-Number (%) of Patients

	Placebo	OXN	Total
Randomized	**302**	**299**	**601**
Randomized and treated (full analysis population)	**302**	**298**	**600**
Completed period on study drug	181 (60%)	218 (73%)	399 (67%)
Discontinued study drug during double-blind period	121 (40%)	80 (27%)	201 (34%)
Adverse event	23 (8%)	24 (8%)	47 (8%)
Subject's choice	8 (3%)	10 (3%)	18 (3%)
Lost to follow-up	1	4 (1%)	5 (1%)
Lack of therapeutic effect	73 (24%)	31 (10%)	104 (17%)
Confirmed or suspected diversion	6 (2%)	5 (2%)	11 (2%)
Administrative	10 (3%)	6 (2%)	16 (3%)
Discontinued study drug and study simultaneously	62 (21%)	48 (16%)	110 (18%)
Adverse event	14 (5%)	15 (5%)	29 (5%)
Subject's choice	8 (3%)	8 (3%)	16 (3%)
Lost to follow-up	1	4 (1%)	5 (1%)
Lack of therapeutic effect	23 (8%)	10 (3%)	33 (6%)
Confirmed or suspected diversion	6 (2%)	5 (2%)	11 (2%)
Administrative	10 (3%)	6 (2%)	16 (3%)
Discontinued study drug and stayed in study	59 (20%)	32 (11%)	91 (15%)
Completed Week 12	49 (16%)	25 (8%)	74 (12%)
Discontinued study prior to Week 12	10 (3%)	7 (2%)	17 (3%)
Adverse event	0	7 (2%)	7 (1%)
Subject's choice	8 (3%)	0	8 (1%)
Lost to follow-up	2 (1%)	0	2

Source: Clinical Study Report, Table 14.1.1.4 and Table 14.1.1.5

In the double-blind phase, subjects were distributed among the OXN dose groups as follows: 10/5 mg: n = 59, 20/10 mg: n = 78, 30/15 mg: n = 69, 40/20 mg: n = 92.

Demographic and baseline characteristics were similar between the treatment groups. The average age was 54 years for both groups, and both groups were predominantly female and Caucasian. The mean pre-randomization pain intensity was 3/10 on the NRS for both treatment groups.

Rescue medication use

During the double-blind period, the percentage of subjects who took, on average, up to two rescue pills per day (oxycodone IR 5 mg) was greater for the placebo group (35%) than the OXN group (28%). Four percent of placebo-treated subjects took more than two rescue pills per day compared to 2% of OXN treated subjects.

Statistical Analysis

As stated in Dr. Li's statistical review:

> The primary efficacy outcome was the "average pain over the last 24 hours" at Week 12. The protocol stated that the causal estimand was the difference in the primary efficacy outcome between the placebo and OXN treatment groups at Week 12 for all randomized subjects regardless of study drug compliance. The primary analysis was based on a mixed-model repeated measures analysis (MMRM) and an adaption of a hybrid imputation approach for handling missing data due to dropouts, which assigns high pain scores to discontinuations due to adverse events. The primary efficacy population included the subjects who were randomized and received study drug. The primary analysis only included data while subjects were taking study drug.

Dr. Li was able to replicate the Applicant's statistical analysis of the primary endpoint, which showed that the difference between OXN and placebo at Week 12 for average pain in the last 24 hours was statistically significant.

Table X: Primary Efficacy Analysis Results

Visit	Statistics	Placebo (N=302)	OXN (N=298)	95% CI	P-value
Screening	Mean (SE)	7.1 (0.06)	7.0 (0.06)		
Pre-randomization	Mean (SE)	3.1 (0.06)	3.1 (0.06)		
Week 12	Mean (SE)	4.2 (0.1)	3.7 (0.1)		
Overall Week 12 Difference	Difference	0.5 (0.2)		(0.1,0.8)	0.006

Source: Clinical Study Report, Table 14.2.1; SE: standard error; CI: confidence interval

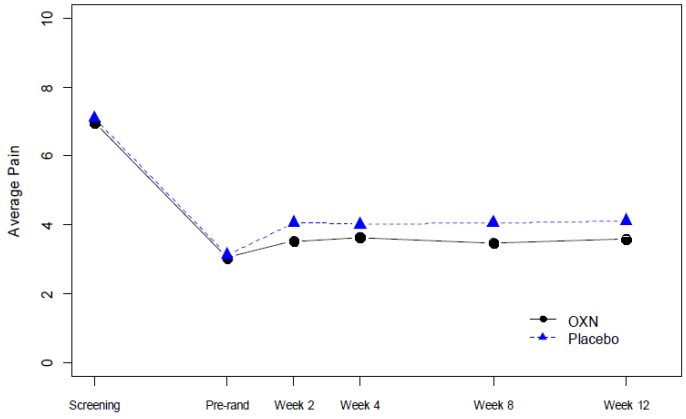
Dr. Li also replicated a number of sensitivity analyses conducted by the Applicant and conducted one additional sensitivity analysis using all observed data including those collected after discontinuation of study drug. The sensitivity analysis results were similar to the primary analysis. Refer to Dr. Li's review for details regarding the sensitivity analyses.

Dr. Li's analyses of the primary endpoint by subgroups; gender, age, and race, did not result in any major or important differences within the groups.

The study was not powered to determine differences in the primary endpoint by dose group, however, there was no clear relationship of the mean "average pain over the last 25 hours" and dose.

Dr. Li constructed a pain curve showing the average pain intensity over time for OXN compared to placebo. It appears that the study effect was roughly maintained from Week 2 to Week 12.

Figure 1: Average Pain Intensity on Study Drug Over Time

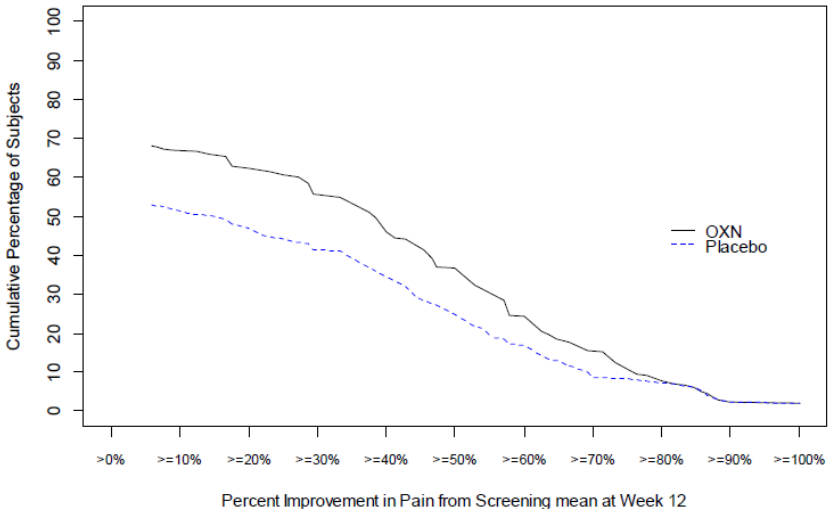


Source: Dr. Li's review, p. 14

Dr. Li also constructed a continuous responder curve, as follows from his review:

> The OXN group also had a better continuous responder curve than the placebo group (Figure 2). For example, about 55% of the subjects in the OXN group had at least 30% improvement from screening. In contrast, approximately 41% of placebo group had at least 30% improvement from screening. Subjects who discontinued study drug were considered as non-responders in the calculations. There was no notable difference between the two treatment groups in the percentages of subjects who achieved more than 80% improvement.

Figure 2: Continuous Responder Curve



Source: Dr. Li's review, p. 15

Secondary Endpoints

The Applicant's analyses of the secondary endpoints, MOS Sleep Scale and PGIC, and additional exploratory endpoints also favored OXN over placebo. These results are supportive, and the Applicant did not request inclusion of these results in the label. Refer to Dr. Kilgore's review for a more detailed discussion of the secondary endpoints.

I am in agreement with Dr. Kilgore's and Dr. Li's findings regarding efficacy for Study ONU3701. Based on review of the conduct of the study and the results of the primary endpoint analysis, with support from the responder analysis and other secondary and exploratory endpoints, this study supports the efficacy of TARGINIC ER in an enriched study population of adults with chronic low back pain requiring treatment with extended-release opioids for a prolonged period of time. This population of patients is representative of the target population of patients with chronic pain, to which these findings may be generalized.

I concur with the review team that the study has demonstrated that Targiniq ER is effective for the agreed upon indicated use.

8. Safety

The following summary of the safety analysis paradigm and exposure data has been reproduced from pages 24 through 26 of Dr. Fields' review:

The Applicant's Integrated Summary of Safety (ISS) was comprised of a complex pooling of 33 clinical studies based on patient population, study design (double-blind vs open-label), study phase, and comparator arms. The majority of the studies, other than the key efficacy study ONU3701, three Phase 1 PK studies, and four abuse liability studies, were conducted outside the US to support registration of OXN in the

EU for the indication of the treatment of pain and OIC. Please refer to Dr. Kilgore's review for additional details regarding the pooling strategy. The most informative pooling for the purposes of this NDA review is what the Applicant refers to as Group A1A which includes two placebo-controlled studies in patients with chronic non-malignant pain (ONU3701 and OXN3401). These studies were similar in design (randomized double-blind, placebo-controlled) and are a subgroup of Group A which includes subjects with chronic nonmalignant or malignant pain. Study OXN3401 was conducted outside the US. Dr. Kilgore reviewed the data from the large pool of 33 studies, as well as Groups A and A1A. Phase 1 studies and the abuse liability studies were reviewed as separate groups.

Exposure

The overall exposure to OXN, in terms of duration of exposure and dose levels appears adequate to inform the safety profile of this product. In the large pool of 33 studies, a total of 3,073 study subjects were exposed to total daily doses of OXN ranging from 10/5 mg to more than 100/50 mg. The average total daily dose of OXN (as oxycodone) was approximately 40 mg. Seven-hundred-ninety-four subjects (26%) were exposed for at least 6 months, and 621(20%) for at least 12 months.

Of the 2396 subjects with chronic nonmalignant or malignant pain (group A), 1084 subjects (45.2%) were exposed to OXN for ≥ 3 months, 794 subjects (33.1%) were exposed to OXN for ≥ 6 months, and 621 subjects (25.9%) were exposed to OXN for ≥ 12 months across all study periods. Of the 2396 exposures, 142 (6%) were exposed to total daily doses of OXN greater than 80/40 mg.

Of the 911 subjects with chronic nonmalignant pain (Group A1A), 460 were exposed to OXN during the double-blind phase of the studies, 168 (37%) for at least 12 weeks. The distribution of exposure by dose in this group is shown in the following Applicant's table. The most common dose was OXN 40/20 mg.

Table 3.3.3
Summary of Cumulative Exposure to OXN During Double-blind by Randomized Total Daily OXN Dose
Population: Randomized Safety – Placebo Controlled Studies in Subjects with Non-malignant Chronic Pain (Group A1A)

Exposure Variable	Total OXN (N=451)	OXN 20/10 (N=124)	OXN 40/20 (N=166)	OXN 60/30 (N=69)	OXN 80/40 (N=92)
Cumulative Exposure Categories, n (%)					
Any Exposure	451 (100.0)	124 (100.0)	166 (100.0)	69 (100.0)	92 (100.0)
>= 1 Week	432 (95.8)	120 (96.8)	163 (98.2)	64 (92.8)	85 (92.4)
>= 2 Weeks	423 (93.8)	119 (96.0)	160 (96.4)	62 (89.9)	82 (89.1)
>= 4 Weeks	397 (88.0)	116 (93.5)	152 (91.6)	57 (82.6)	72 (78.3)
>= 6 Weeks	380 (84.3)	111 (89.5)	148 (89.2)	53 (76.8)	68 (73.9)
>= 8 Weeks	361 (80.0)	107 (86.3)	140 (84.3)	50 (72.5)	64 (69.6)
>= 10 Weeks	335 (74.3)	103 (83.1)	127 (76.5)	47 (68.1)	58 (63.0)
>= 12 Weeks	172 (38.1)	60 (48.4)	71 (42.8)	17 (24.6)	24 (26.1)
Cumulative Days of Exposure					
n	451	124	166	69	92
Mean (SD)	69.9 (24.98)	75.3 (21.59)	72.8 (22.01)	64.4 (27.99)	61.8 (29.09)
Median	82.0	83.0	83.0	79.0	78.0
Min, Max	1, 123	4, 123	1, 93	4, 89	1, 92
Average Total Daily Oxycodone Dose (mg)					
n	298	59	78	69	92
Mean (SD)	49.5 (22.36)	19.7 (0.51)	37.4 (8.22)	56.9 (7.61)	73.5 (14.36)
Median	53.3	19.9	39.7	59.5	79.4
Min, Max	10, 80	17, 20	19, 80	20, 60	10, 80

Note: Cumulative exposure is defined as the total number of days the subject is exposed to OXN during double-blind. OXN dose is presented as total daily oxycodone dose in mg.
Studies in Group A1A: ONU3701 and OXN3401. Study OXN3401 is excluded from average total daily dose calculation due to the inconsistent recording of dose in this study.

Disposition

Of the 3073 subjects exposed to OXN, 33% discontinued treatment at some point during the studies. The most common reason for discontinuation was adverse event (10%), followed by lack of therapeutic effect (6%). There were no unexpected findings in terms of disposition of patients in the safety database.

The following summary of the death data from the application has been reproduced from page 27 of Dr. Fields' review:

> Across the studies of chronic nonmalignant or malignant pain (Group A study pool), there were 57 deaths; a total of 42 deaths occurred in 2,396 subjects during or after exposure to OXN. There were 13 deaths that occurred in patients treated with oxycodone controlled-release, one treated with oxycodone IR, and one in a placebo patient. Fifty-one of the 57 deaths occurred in Study OXN2001 and were mainly the result of tumor progression in cancer patients. One death occurred in the key efficacy study ONU3701 in a patient randomized to placebo treatment.
>
> Dr. Kilgore reviewed all of the narratives, and noted two deaths may have possibly been related to study drug. One was a 61 year old male with metastatic cancer who after eight days of treatment with OXN (titrated from 30/15 mg to 90/45 mg during that period) complained of headache and dizziness, followed by death later in the day. The death was coded as heart and circulation failure, and the narrative also stated the patient had a pulmonary embolism and intracerebral bleed (timing not clear). However, the pulmonary embolism and intracerebral bleed appear to have been the cause of death, not the study drug.
>
> The second death occurred in a 55 year old male with metastatic lung cancer who died after treatment with OXN for 10 days at increasing doses up to 80/40 mg total daily dose. Dr. Kilgore felt that contribution of the study drug to death could not be ruled out.
>
> Three deaths on OXN occurred in non-cancer patients, and all appear unrelated. Causes of deaths were traffic accident, necrotizing faciitis, and sepsis.

The following summary of the non-fatal serious adverse events and discontinuations due to adverse events was reproduced from pages 27 through 29 of Dr. Fields' review:

> Nonfatal Serious Adverse Events
>
> Dr. Kilgore reviewed the nonfatal SAEs and noted that 7% of the 3,073 subjects exposed to OXN experienced at least one event, the most common being neoplasms, gastrointestinal, and connective tissue disorders, all at 1%. In the double-blind, placebo-controlled studies in nonmalignant pain patients, the incidence of SAEs was 6% in OXN-treated subjects, and 3% in placebo subjects. Drug screen positive and abdominal pain were the only SAE terms that occurred in more than two subjects in either treatment group. Of note, there were two MIs in the OXN group compared to none in the placebo group. An in depth review of the cardiac safety findings for OXN was conducted by the Division of Cardiorenal Products and no cardiac safety signal was identified. The consult response is discussed later in this section.

MedDRA System Organ Class Preferred Term	Placebo (N=460) n (%)	OXN (N=451) n (%)
Subjects With Any Nonfatal Serious Adverse Events	**14 (3.0)**	**26 (5.8)**
Cardiac Disorders	**2 (0.4)**	**3 (0.7)**
Atrial fibrillation	0 (0.0)	2 (0.4)
Acute myocardial infarction	2 (0.4)	0 (0.0)
Gastrointestinal Disorders	**1 (0.2)**	**5 (1.1)**
Abdominal pain	1 (0.2)	3 (0.7)
Nausea	0 (0.0)	2 (0.4)
Vomiting	0 (0.0)	2 (0.4)
Investigations	**2 (0.4)**	**11 (2.4)**
Drug screen positive	1 (0.2)	9 (2.0)
Social Circumstances	**2 (0.4)**	**0 (0.0)**
Substance use	2 (0.4)	0 (0.0)

MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone/naloxone controlled-release tablets.
Note: Adverse events are treatment-emergent events and coded with MedDRA Version 15.0. Adverse events are sorted alphabetically by system organ class and by descending frequencies in the OXN column. Multiple occurrences of the same adverse event in one individual are counted only once.

Source: Applicant's ISS, p. 176

In Study ONU3701, the incidence of SAEs during the open-label titration period where all subjects were treated with OXN was 1% (9 subjects with 16 events), and in the double-blind period was 4% in placebo subjects and 6% in OXN treated subjects. For nine of the 11 subjects in the open-label titration period, abuse-related terms were reported, e.g., drug screen positive, drug abuse, and drug overdose. For the remaining subjects, Dr. Kilgore determined that two events (dehydration/vomiting, and worsening esophageal stricture) may have been related to OXN. In the double-blind period, 4% of placebo and 6% of OXN treated subjects experienced SAEs. One SAE of rectal perforation was determined by the investigator not to be related to OXN, however, Dr. Kilgore could not rule out an association with study drug. While the subject had a long-term history of constipation, OXN may have contributed to both the continued constipation and hence the SAE.

Overall there were no trends or unexpected findings in the review of the SAEs that would require the addition of labeling language not already proposed by the Applicant.

Discontinuations due to AEs

Overall, the pattern of discontinuations due to adverse events was consistent with the known safety profile of opioid analgesics observed in clinical trials.

Of the 3073 subjects exposed to OXN, 280 (9%) discontinued treatment due to AEs. The most commons types of AEs were in the System Organ Class (SOC) for Gastrointestinal Disorders (3%) and Nervous System Disorders.

In the double-blind, placebo-controlled studies in subjects with non-malignant pain (Group A1A), rates of discontinuation due to AEs were similar in the OXN-treated (6%) and placebo-treated (7%) subjects. Types of adverse events were similar to those in the larger database, however the GI disorders occurred slightly more commonly in the placebo group (2%) compared to OXN-treated subjects (1.3%). Also, 3% of subjects in the OXN group discontinued due to drug screen positive, compared to 1% in the placebo-treated group.

In Study ONU3701 during the open-label titration) period, the incidence of discontinuation adverse events was higher in the non-randomized (18%) compared to randomized (<1%). The study was designed so that those subjects who could not tolerate study drug were not randomized. For those subjects who discontinued during the open-label titration period and were not randomized, the highest incidence of AEs occurred in the GI SOC (7%) with the preferred terms, nausea (5%), vomiting (2%),

abdominal pain upper (2%) and diarrhea (1%). Of note, one subject treated with OXN discontinued treatment because of angioedema after eight days of treatment.

In the double-blind period, adverse events leading to discontinuation occurred with nearly equal incidence for placebo and OXN, being approximately 7% for both. Drug screen positive accounted for the highest incidence in OXN (4%). When drug screen positive is not included, the highest incidence of discontinuation AEs occurred in the GI SOC with an overall low incidence (1%) in both placebo and OXN groups.

Dr. Kilgore also concluded that the common adverse event profile of Targiniq ER was consistent with the opioid class of drugs. There were no unusual or unexpected findings from the analyses of vital signs, ECGs or laboratory data. The following summary of the review team's exploration into two types of adverse events of special interest, opioid withdrawal and cardiovascular safety, has been reproduced from pages 30 through 35 of Dr. Fields' review:

Opioid Withdrawal
Study ONU3701 was prospectively designed to assess the occurrence of opioid withdrawal symptoms in subjects treated with OXN compared to placebo. Although the presence of naloxone in TARGINIC ER is for the purpose of conveying abuse-deterrent properties, there is the possibility that patients treated with this product may be at risk for adverse events due to the naloxone, specifically opioid withdrawal (OW). The occurrence of OW was assessed in several ways in Study ONU3071:

- Investigator identified OW adverse events of drug withdrawal or withdrawal syndrome (Investigators were required to evaluate all subjects who reported COWS scores ≥5 or SOWS scores ≥ 10 to determine if an AE of opioid withdrawal occurred)
- Prospective, blinded, independent adjudication committee review based on a) COWS score ≥ 13; b) AE of opioid withdrawal recorded by the investigator in the CRF; c) three or more criteria of opioid withdrawal as defined by the DSM-IV diagnostic criteria occurring within a span of 7 days; and/or 4) committee member clinical judgment.
- Plasma concentrations of oxycodone, naloxone, and naloxone-3β gluronide collected at prerandomization (Visit 3), midtreatment (Visit 6), end of treatment (visit 8), and while in opioid withdrawal

Dr. Kilgore extensively reviewed the Applicant's analyses, and arrived at the following conclusions:

> The Applicant maintains that most cases of opioid withdrawal in OXN-treated patients occurred during times of transition (i.e., changes in morphine equivalents up or down). Although opioid withdrawal occurred in Study ONU3701 in OXN-treated subjects when: 1) Transitioning from their original, non-study opioid to OXN in the open-label titration (OLT) period, 2) Titrating to a higher or lower dose of OXN in the open label titration period, 3) Titrating OXN during the Double-blind period or transitioning to placebo from OXN, and 4) Transitioning from their OXN dose to their original opioid treatment at the end of the study, opioid withdrawal occurred at other times as well. However, I agree with the Applicant's assessment that most cases of OW occurred during times of transition as summarized below:

Forty-three OW events (Investigator identified plus Adjudication Committee identified)

- Open-label treatment (OLT)
  - 56% occurred during the OLT period
  - 62% of those in the OLT period occurred when morphine equivalents were being decreased during a transition
- Double-blind (DB)
  - 44% occurred during the DB period
  - 63% of those in the DB period were in TARGINIC ER-treated subjects
    - 58% occurred when dose was being decreased (7 events); 42% when dose was unchanged (5 events)
    - Most (58%) occurred in patients taking OXN 80/40 mg

Dr. Kilgore stated that it is not unexpected that when a subject is transitioned to a dose of OXN that is lower in morphine equivalents than their previous opioid, that symptoms of opioid withdrawal could occur. Therefore the events of interest are the five withdrawal events that occurred in the double-blind period where morphine equivalent doses were unchanged. This is a relatively small number of events, however, it does support the concept that opioid withdrawal symptoms may occur in patients treated with TARGINIQ ER. The product label will include appropriate language regarding the possibility of occurrence of withdrawal in patients.

Regarding the analysis of plasma concentrations of oxycodone, naloxone, and naloxone-3β gluronide collected at prerandomization (Visit 3), midtreatment (Visit 6), end of treatment (visit 8), and while in opioid withdrawal, Dr. Kilgore writes

- In an analysis conducted in pivotal study ONU3701, there were no clear differences in the distribution of naloxone concentrations between subjects with or without opioid withdrawal symptoms, regardless of OXN dose.

Cardiovascular Safety

Prior to NDA submission, the Division requested that the Applicant conduct an analysis of OXN safety data in order to determine whether there is a cardiac safety signal for TARGINIC ER. A peripheral opioid antagonist drug intended for the treatment of opioid-induced constipation, Alvimopan, was noted to have an excess of cardiovascular events in its clinical trial database, and an AC was held in 2008 to discuss the issue. Since then, other peripheral opioid antagonists have been developed for the treatment of OIC, and the question has arisen as to whether there is a class effect in terms of a cardiac signal. There is also a question as to whether opioid withdrawal may be associated with the occurrence of cardiac events. Therefore, the Applicant for TARGINIC ER was asked to conduct these analyses. The Division of Cardiovascular and Renal Products (DCaRP) and the Division of Biometrics VII (DB VII) were consulted by DAAAP to review the Applicant's analyses. The acronym MACE stands for Major Adverse Cardiac Events which, in general, include MI, stroke, and cardiac death. The cardiac events were collected as part of routine safety monitoring in the clinical trials, and not from trials prospectively designed to assess CV safety.

Dr. Preston Dunmon (DCRP) provided the following conclusions, however noted several limitations to the analysis in his review. These included the distinct patient populations that were integrated for the assessment, differences in study design,

different dosing regimens, the and the relatively high baseline risk of cardiac events in the study populations. Please refer to Dr. Dunmon's review for additional details of his analyses.

1. Assessment of whether there appears to be a signal for cardiac adverse events associated with the use of OXN (including the type and extent of the signal if present), the following are relevant:

   MACE events were more frequent in the comparator arms as compared to the OXN treatment arms of both pooled GroupA1A (placebo controlled trials) and Group A1C (OXY CR-controlled trials). Exposure-corrected non-MACE cardiovascular adverse event rates were similar between OXN and comparator-treated patients. (See table 17, page 16 of this review). These observations are limited by the very high percentages of antecedent dropouts in the run-in periods, high censoring rate of premature withdrawals, sub-optimal CV event ascertainment in all trials, and the brief duration of follow-up in these short studies.

   While no TQT study was performed with the OXN combination, ECG interval analysis from pivotal trial 3701 does not demonstrate a clinically meaningful prolongation of the QT, QTcB, or QTcF.

   While there were numerically more occurrences of atrial fibrillation in OXN-treated patients (by one or two cases, depending on the analysis), the numbers are too small to draw any conclusions.

   Thus, no signals for excess MACE, non-MACE CV AEs, or repolarization/conduction system toxicity with OXN are identified from these studies.

2. An assessment of whether there is a causal relationship between cardiac events that occurred and opioid withdrawal.

   OXN appears to be associated with elevations of both SBP and DBP in patients previously treated (presumably for hypertension, see table page 33 of this review),and hypertensive AEs occurred. Of the nine patients experiencing an SMQ-based CV AE and opioid withdrawal symptoms in the overall population (Group C) during any study period, three of the nine experienced blood pressure elevations in close proximity to OXN dosing, one of which was a hypertensive crisis. There were no concomitant AEs involving BP elevation with withdrawal symptoms in any comparator group. Though the numbers of subjects in which a CV AE/SAE occurred within 28 days of withdrawal symptoms was small, the hazard ratio for the time to first CV SAE was 14 times higher in patients with opioid withdrawal symptoms within 28 days (p=0.0006), and 5 times higher for the time to first non- serious CV AE in patients with opioid withdrawal symptoms within 28 days (p=0.0014), regardless of treatment (see page 28 of this review).

   From a mechanistic point of view, the above observations should be interpreted in the context of an understanding of the determinants of myocardial oxygen demand. Opioid withdrawal induces physiologic stress in some patients. This

physiologic stress will increase myocardial work and myocardial oxygen demand. Any drug, device, or procedure that induces physiologic stress has the potential for causing destabilization in patients with tenuous coronary perfusion and/or important stenotic valvular heart disease (these are not "confounders"). These are basic principles of medicine that apply to many approved therapies, and for which clinical judgment of the treating physician is important. In the overall target populations of all of these therapies, however, this risk is small.

Other DCaRP Comments/Recommendations

It is unclear what if any relevance that the side effect profile of IV naloxone has to the clinical safety profile of this oral oxycodone + naloxone combination. However, given the lack of clinical experience with OXN in post-operative patients, it would be reasonable to at least reference the warning about these patients from the IV naloxone label (i.e., that several instances of hypotension, hypertension, ventricular tachycardia
and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients treated with IV naloxone).

Language reflecting the above recommendation will be included in the TARGINIC ER label.

Janelle Charles, Ph.D. of DB VII provided a statistical review of results from the Applicant's analyses of the clinical trial database and results from assessments from other data sources, such as European postmarketing databases. She states in her review that a definitive conclusion that there is no CV safety concern with OXN cannot be made from the data sources evaluated in her review. Therefore, if there is need to further characterize the CV risk of OXN, further assessment may be conducted postmarketing, if it is approved. Please refer to Dr. Charles review for additional details.

Based on the reviews conducted by DCaRP and DB VII, there does not appear to be evidence of a cardiac signal in the clinical trial or postmarketing analyses submitted by the Applicant. In all double-blind trials combined, there were two SMQ-based MACE events (0.2%) in subjects treated with OXN, and seven (0.6%) in comparator-treated subjects. None of the MACE events in OXN-treated subjects occurred in Study ONU3701. However, there are several limitations of the analyses. Findings from the analysis of CV events will not be included in the TARGINIC ER label, as recommended by Dr. Charles.

I concur with the review team that no new or unexpected safety signals have been demonstrated during this development program.

9. Advisory Committee Meeting

The following summary of a recent meeting of the Anesthetic and Analgesic Drug Products Advisory Committee convened to address concerns regarding the cardiovascular toxicity of peripherally-acting mu opioid receptor antagonists has been reproduced from page 36 of Dr. Fields' review:

An Advisory Committee meeting was not convened specifically for this application. However, on June 11-12, 2014, the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met to discuss the potential cardiovascular risk associated with products in the class of peripherally-acting mu opioid receptor antagonists (PAMORAs) and the necessity, timing, design, and size of cardiovascular outcome trials to support approval of products in this class (b) (4) in patients taking opioids for chronic pain. The occurrence of opioid withdrawal and its potential contribution to a cardiac signal was also discussed. The impetus for this meeting, conducted by DGIEP, was an imbalance in cardiac events that occurred during development of alvimopan (Entereg), for which an Advisory Committee meeting was held in 2008. The resulting indication for alvimopan was short-term use to accelerate time to upper and lower GI recovery following surgeries. (b) (4).

AADPAC generally agreed that controlled cardiac outcome trials are not needed for this class of drugs (b) (4) due to lack of a clear cardiac signal during development programs. Some members of the panel thought that it may be reassuring to collect post marketing data on cardiac safety via observational studies in order to rule out a large increase in MACE risk.

Although TARGINIC ER is not being approved for the treatment of OIC, and the naloxone component does not act entirely peripherally (the Applicant states there is local action in the GI tract as well as <2% absolute BA largely due to extensive first-pass metabolism, enters the CNS), the effects of this product on cardiovascular safety would be expected to the be same as the PAMORA class of drugs intended for the treatment of OIC, and the intended population of patients with chronic pain requiring around-the-clock treatment with an extended-release opioid is essentially the same as the OIC population. Both oxycodone and naloxone are approved drugs and have a long history of use. The Applicant has provided a large amount of safety data for oxycodone/naloxone in the target population, marketed as Targin outside the U.S. The long history of use and the large safety database provide reassurance regarding the absence of a strong cardiac signal for TARGINIQ ER. Therefore, as per the recommendation of the AADPAC, and to maintain consistency within this class of opioid antagonists, a post marketing requirement will be imposed on the Applicant such that they must conduct an observational study or studies to further assess the risk of major cardiac adverse events in patients treated with TARGINIC ER. The observational study may provide information on whether there is a large excess risk of cardiac events with this drug.

10. Pediatrics

The following summary of the pediatric issues related to this application has been reproduced from page 37 of Dr. Fields' review:

As a new combination product that triggers PREA, pediatric studies are required for TARGINIC ER. For extended-release opioid analgesics intended for the treatment of chronic pain, pharmacokinetic and safety studies are required for the age group 7 to 17 years. Efficacy findings from adults can be extrapolated to this age group as the underlying conditions are similar in children and adults, and the exposure response to opioids is expected to be similar in the two groups.

The following pediatric plan was reviewed by the Pediatric Research Committee (PeRC) on May 28, 2014, and agreed upon with the Applicant to be performed as a post-marketing commitment:

> Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of oxycodone hydrochloride/naloxone hydrochloride extended-release tablets in patients from ages 7 to less than 17 years pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
>
> | | |
> |---|---|
> | Final Protocol Submission: | December 31, 2014 |
> | Study Completion: | December 31, 2018 |
> | Final Report Submission: | June 30, 2019 |

11. Other Relevant Regulatory Issues

As the adequacy of the abuse-deterrent features of Targiniq ER is the key aspect of this application in regard to marketing claims and the overall risk-benefit profile of the product, I have reproduced the conclusions and recommendations from pages 2 through 7 of Dr. Tolliver's review in total below:

> **Conclusions:**
>
> Following a review of all information submitted under NDA 205-777, CSS provides below conclusions regarding Targiniq ER tablets.
>
> 1. Overall, the data provided from in vitro physical and chemical manipulation studies and human abuse potential studies indicate that Targiniq ER tablets display resistance to abuse by intravenous and intranasal administration, but to a lesser extent to oral administration, depending upon the abusing population.
>
> 2. For the population of non-dependent, non-tolerant recreational opioid users manipulation (crushing or extraction from whole tablets in hot water) of Targiniq ER tablets with the intention of intravenous or intranasal administration will most likely result in little or no drug liking due to the presence of naloxone (study ONU1003) in a 2:1 ratio of oxycodone HCl/naloxone HCl that suppresses the mu-opioid agonist effects of oxycodone. However, such individuals may be expected to experience substantial levels of drug liking as well as possible overdose when Targiniq ER tablets are crushed followed by ingestion or when chewed followed by swallowing (see Study ONU1007). This may be attributed to the very low ($\leq$ 2%) absolute oral bioavailability of naloxone as well as to the extensive compromise of the controlled release mechanism for oxycodone HCl and naloxone HCl upon crushing (including crushing by chewing) of Targiniq ER tablets.

3. For the population that is physically dependent and tolerant to opioids, manipulation of Targiniq ER tablets (crushing or extraction from whole tablets in hot water) following by intravenous or intranasal administration will likely elicit a prominent withdrawal syndrome, depending upon the level of physical dependence. With oral administration of crushed Targiniq ER tablets or with chewing of Targiniq ER tablets followed by swallowing, individuals physically dependent and tolerant to opioids will likely experience limited, if any, drug liking. (See Study ONU1008). This may be attributed to the reduced sensitivity of this population to opioid subjective effects as a result of tolerance and to the emergence of at least some levels (mild) of withdrawal.

4. The results of vitro studies indicate that "opioid-naïve or opioid non-tolerant patients" who are initiated with Targiniq ER tablets, may be at risk of potential overdose should they administer orally crushed Targiniq ER tablets or chew Targiniq ER tablets. Likewise, patients who are physically dependent to opioids (Targiniq ER or other opioid medications) and orally administer crushed Targiniq ER tablets or chew Targiniq ER tablets will likely experience a withdrawal syndrome, the severity of which will depend upon the level of physical dependence.

5. The principal mechanisms underlying the abuse deterrent properties of Targiniq ER tablets are a) the difficulty involved in separating the naloxone HCl from the oxycodone HCl as evidenced in various in vitro studies and b) the effectiveness of the 2:1 ratio of oxycodone HCl to naloxone HCl in blocking the subjective reinforcing effects of oxycodone and potentially precipitating withdrawal.

6. (b) (4)

7. (b) (4)

(See Discussion, Tables 1, 2, and 3)

8. (b) (4)

(b) (4)

(See Discussion, Tables 1, 2, and 3)

9. (b) (4)

(See Discussion, Tables 2 and 4)

10. Dissolution studies demonstrated that whole Targiniq ER tablets do not dose dump oxycodone HCl and naloxone HCl in simulated gastric fluid containing 40% ethanol. (See Discussion, Table 5)

11. (b) (4)

12. (b) (4)

13. Results of simulated smoking studies indicate that Targiniq ER tablets most likely cannot be abused by smoking. (b) (4)

14. (b) (4)

(b) (4)

15. (b) (4)

(See Table 7)

16. (b) (4)

17. (b) (4)

18. Human abuse potential study ONU1003, using non-dependent opioid experienced subjects, demonstrated that the intravenous injection of 0.035 mg/kg naloxone HCl followed within 1 minute by intravenous injection of 0.07 mg/kg oxycodone HCl solution (simulated 2:1 ratio of oxycodone HCl to naloxone HCl as found in Targiniq ER tablets) produced maximum levels of Drug Liking and High that were similar to that produced by placebo (0.9% NaCl), but well below that produced by oxycodone HCl 0.07 mg/kg solution. In the absence of significant differences in oxycodone HCl plasma levels obtained for the two active treatments, the differences in subjective effects observed, indicate that the 0.035 mg/kg naloxone HCl was effective in reducing the subjective effects of the 0.07 mg/mg oxycodone HCl. The efficacy of the abuse deterrent effect by intravenous administration is also demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following intravenous injection of the oxycodone HCl and naloxone HCl combination, as compared to injection of just oxycodone HCl. (See Discussion, Tables 9 and 11)

19. Human abuse potential study ONU1003, using non-dependent, opioid-experienced subjects, demonstrated that insufflation of finely crushed Targiniq ER 40/20 mg resulted in maximum Drug Liking and High that were substantially lower than that produced by insufflation of oxycodone HCl 40 mg powder but similar to that of placebo for Drug Liking and higher than placebo for High. As evidenced by scores on the Take Drug Again VAS, the willingness of subjects to insufflate oxycodone HCl 40 mg powder again was much higher than the willingness to take either crushed Targiniq ER 40/20 mg or placebo. The maximum oxycodone plasma concentration (C_{max}) tended to be higher following crushed Targiniq ER than with oxycodone HCl powder alone, with both having similar short time to C_{max} of about 1 hour. The efficacy of the abuse deterrent effect to intranasal administration is also demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following intranasal administration of Targiniq ER compared to the positive comparator. Again, these data suggest the effectiveness of the naloxone HCl in the Targiniq ER formulation in

mitigating the subjective reinforcing effects of oxycodone HCl. (See Discussion, Tables 9 and 10)

20. Human abuse potential study ONU1007, using non-dependent, opioid-experienced subjects, demonstrated that in comparison to oxycodone 40 mg oral solution (active comparator), chewed Targiniq ER 40/20 mg produced similar maximum levels of Drug Liking, High and Take Drug Again. Ingestion of intact Targiniq ER 40/20 mg produced significantly lower levels of Drug Liking, High, and Take Drug Again that were, however, significantly above placebo. The maximum oxycodone plasma level (C_{max}) tended to be similar between chewed Targiniq ER 40/20 mg and oxycodone 40 mg oral solution with a similar median time of C_{max} of 1.05 hours. With ingestion of intact Targiniq ER 40/20 mg, the oxycodone plasma level was a little less than half that of chewed Targiniq ER 40/20 mg Treatment with intact or chewed Targiniq resulted in only low maximum plasma levels of naloxone, reflecting the very low oral bioavailability ($\leq$ 2%) of naloxone. The high levels of subjective reinforcing effects with chewed Targiniq ER may be attributed to the low levels of naloxone available to antagonize the effects of oxycodone following oral. The lower but still significant levels of subjective effects following ingestion of intact Targiniq ER is most likely due to the controlled release properties of the intact formulation for oxycodone HCl. (See Discussion, Tables 12 and 13)

21. Sponsor conducted human abuse potential study ONU1004 to evaluate the subjective effects of chewed Targiniq ER 30/15 mg and chewed Targiniq ER 60/30 mg in opioid dependent (methadone maintained) subjects. However, a review conducted by the Office of Biostatistics found that with respect to Drug Liking VAS there were no significant differences between 30 mg or 60 mg oxycodone HCl solution (active comparator) and placebo. As such, the Office of Biostatistics concluded that differences between chewed Targiniq ER (either dose) and oxycodone HCl oral solution were not meaningful. A statistical analysis was completed regarding withdrawal scores using the "Subjective Opioid Withdrawal Scale" (SOWS). Subjects treated with Targiniq ER 60/30 mg had a similar maximum SOWS score compared to placebo but significantly high maximum SOWS score compared to oxycodone HCl 60 mg active solution. Only two subjects had a mean maximum SOWS above 10 with the highest being 14, indicating moderate withdrawal.

22. Human abuse potential study ONU1008 demonstrated that opioid dependent, methadone-maintained subjects may be less susceptible to oral abuse, including chewing, of Targiniq ER tablets. This may be due to the presence of tolerance to subjective effects (less sensitivity) and to experiencing the adverse effects of withdrawal. Intact and chewed Targiniq ER 60/30 mg tablets produce similar low levels of Drug Liking and High that were similar to placebo, but significantly lower than that produced by the active comparator oxycodone 60 mg oral solution. The Take Drug Again VAS demonstrated a limited willingness of subjects to take again oxycodone 60 mg oral solution but a desire not to take again either placebo, intact Targiniq ER or chewed Targiniq ER. Data provided by Sponsor showed that chewed Targiniq ER 60/30 mg and oxycodone 60 mg oral solution produced similar maximum oxycodone plasma levels reached at a median of 1.08 and 2.07 hours, respectively. With intact Targiniq ER 60/30 mg maximum oxycodone

plasma level was a little less than half that of chewed Targiniq ER and positive comparator with a median time of 3.05 hours. Chewed and intact Targiniq ER treatments resulted in low levels of naloxone in plasma reflecting the poor bioavailability of naloxone following oral administration. The efficacy of the abuse deterrent effect by oral administration on opioid dependent subjects is further demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following treatment with either intact Targiniq ER tablet or chewed Targiniq ER tablet compared to treatment with the positive comparator. (See Discussion, Tables 14 and 15)

23. In human abuse potential study ONU1008, the use of the "Subjective Opioid Withdrawal Scale" (SOWS) (64 point scale) revealed that for all treatments there were opioid dependent (methadone-maintained) subjects who displayed withdrawal, most often mild withdrawal. Treatment with chewed Targiniq ER produced the maximum SOWS scores that, according to Sponsor, were significantly greater than those observed following treatment with placebo, intact Targiniq ER, or oxycodone HCl 60 mg oral solution. Individual subject data revealed that of 29 total subjects, 20, 22, 23, and 19 subjects displayed "mild withdrawal" (SOWS scores 1-10) following treatment with intact and chewed Targiniq ER, oxycodone HCl 60 mg oral solution, and placebo, respectively. Two and 6 subjects displayed severe withdrawal (SOWS score of > 20) following intact and chewed Targiniq ER, respectively. Three and 2 subjects, following placebo displayed moderate (SOWS score 11-20) and severe withdrawal, respectively.

24. As part of the safety assessment Sponsor provided eight case narrative reports obtained from an international drug safety database (manufacturer's adverse effects reporting database: ARGUS) documenting severe withdrawal with hospitalization in subjects who attempted to manipulate (crush) and abuse (intravenous or snorting) oxycodone/naloxone (2:1 ratio) product (i.e., Targin) currently marketed in other countries. (See Discussion, Integrated Assessment)

Recommendations:

1. Sponsor should be required to carefully monitor for the oral abuse and potential concomitant overdose of crushed Targiniq ER tablets particularly among recreational opioid users who may manifest a lack of or low level of physical dependence and opioid tolerance. Due to the very low bioavailability of naloxone and to the compromise of the controlled release mechanism of oxycodone HCl and naloxone HCl upon crushing, crushed (including chewed) Targiniq ER tablets are expected to produce high levels of subjective reinforcing effects, analogous to immediate release oxycodone formulation, following ingestion. This outcome is supported by the results of human abuse potential study ONU1007 in which non-dependent subjects chewed Targiniq ER tablets resulting in high levels of Drug Liking.

2. The label should contain clear warnings of possible precipitated withdrawal occurring in individuals who are opioid dependent and purposely attempt to intravenously or intranasally abuse Targiniq ER tablets after crushing.

Withdrawal may also be observed in opioid-dependent subjects who attempt to chew Targiniq ER tablets.

3. The language proposed by the Sponsor in Section 9.2 of the label regarding "In Vitro Testing" is appropriate and should be included in the label. This language affirms the results of in vitro testing, namely that although with crushing the controlled release mechanisms are compromised for both oxycodone HCl and naloxone HCl, it is very difficult to use physical and chemical manipulations to separate the naloxone from the oxycodone.

The proposed inclusion of language describing human abuse potential studies ONU1003 and ONU1008 should be granted.

This summary of the impact of manipulation of the abuse-deterrent features of Targiniq ER was presented by Dr. Tolliver at the Wrap-Up Meeting for the application and has been reproduced from page 45 of Dr. Field's review:

Non-Dependent, Non-Tolerant Recreational Opioid Users Who Attempt to Manipulate TARGINIC ER for Purposes of Abuse (Example: Teenagers from medicine cabinet or from friends)

- I.V. Crushed or Intact TARGINIC ER – Little or No Drug Liking
- I.N. Crushed TARGINIC ER – Little or No Drug Liking
- Crushed Oral TARGINIC ER – SUBSTANTIAL Drug Liking + Possible Overdose
- Chewed (Crushed) Oral TARGINIC ER – SUBSTANTIAL Drug Liking + Possible Overdose

Opioid Dependent, Opioid Tolerant Users Who Attempt to Manipulate TARGINIC ER for Purposes of Abuse

- I.V. Crushed or Intact TARGINIC ER – Likely WITHDRAWAL
- I.N. Crushed TARGINIC ER – Likely WITHDRAWAL
- Crushed Oral TARGINIC ER – Limited if Any Drug Liking, Possible Withdrawal
- Chewed (Crushed) Oral TARGINIC ER – Limited if Any Drug Liking, Possible Withdrawal

The review team and I concur with Dr. Tolliver's conclusions and recommendations.

12. Labeling

The review team and the Applicant have reached agreement on all aspects of the product labeling. There were no aspects of the labeling that required extensive or difficult negotiations between the Applicant and the review team.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The Applicant has provided sufficient data to support the efficacy, safety and quality of Targiniq ER for marketing. As an extended-release, high potency opioid product, it will fall under the requirements of the ER/LA Opioid REMS. Purdue has demonstrated that Targiniq ER's formulation provides a sufficient level of abuse-deterrence for the intravenous and intranasal routes of abuse that appropriate language in the product labeling is indicated to provide guidance to prescribers and patients. Without comparative data, it's not possible to know whether the level of abuse deterrence provided by Targiniq's formulation is better than, equal to, or less than that of OxyContin-reformulated. Therefore, both products will be available on the market at the same time unless and until one of them has proven to be sufficiently less abusable such that we could consider requiring the other to be removed from the market. There are advantages to having both products available as it is well established that there is great inter-patient variability in tolerance to drugs within a class, in general, and particularly with the opioid drugs. The addition of one or the other set of abuse-deterrent features could decrease the tolerability of that product for some patients. In addition, we can't really know whether one or the other of these products provides more or less abuse-deterrence until they have been adequately tested in the real world setting. It is also important to note that neither product provides any deterrence to abuse by the oral route, a common form of abuse that can still lead to addiction, overdose and death. Therefore, prescribers must still maintain appropriate discretion in choosing to treat a patient with Targiniq ER, and careful monitoring of their patients being treated with Targiniq ER.

  Appropriate labeling has been provided, and educational efforts will be necessary to inform prescribers regarding the limitation on the upper dose of Targiniq, in order to avoid the adverse events that were seen in opioid-tolerant patients at total daily doses higher than 80/40 mg. Due to the possibility, based on studies from other drugs in this class, that peripherally-active, mu-opioid antagonists can cause cardiovascular

thromboembolic toxicity in some patients, the Applicant will be required to perform a postmarketing study to further evaluate this effect in patients treated with Targiniq ER.

- Postmarketing Risk Management Activities

  The approved Targiniq ER application must adhere to the requirements of the ER/LA Opioid REMS.

- Postmarketing Study Requirements

  The following summary of the post-marketing study requirements has been reproduced from pages 50 through 54 of Dr. Fields' review, with the exception of the final PMR which was added after Dr. Fields filed her review:

  1. Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of oxycodone hydrochloride/naloxone hydrochloride extended-release tablets in patients from ages 7 to less than 17 years pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

     Final Protocol Submission: December 31, 2014
     Study Completion: December 31, 2018
     Final Report Submission: June 30, 2019

  2. We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of misuse, abuse, addiction, hyperalgesia, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which TARGINIQ ER is a member. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

     Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

     2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

     These studies should address at a minimum the following specific aims:

     a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and

duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:
The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission:	08/2014
Study Completion:	01/2018
Final Report Submission:	06/2018

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	11/2015

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015

Final Report Submission: 11/2015

2065-4 Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	11/2015

Please note the following considerations regarding the postmarketing requirements detailed above. Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate. Because many of the risk factors for misuse, abuse, addiction, overdose, and death cannot be captured using administrative databases alone, FDA is unlikely to find adequate protocols or strategies that evaluate administrative databases only as meeting the objectives outlined above.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioids, of which TARGINIQ ER is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this trial:

Final Protocol Submission:	08/2014
Trial Completion:	08/2016
Final Report Submission:	02/2017

We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies and clinical trial to provide the best information possible.

3. FDA has determined that, in addition to participation in the PMR studies required of all ER/LA opioid analgesic application holders listed above, you are required to conduct the following individual post-marketing studies of Targiniq ER (Oxycodone hydrochloride and naloxone hydrochloride) extended release tablets.

XXXX-1: Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of Targiniq ER (Oxycodone hydrochloride and naloxone hydrochloride) extended release tablets actually result in a significant and meaningful decrease in misuse and abuse, and their consequences addiction, overdose, and death in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Targiniq ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013)[1], and proposed study populations and drug comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	7/2015
Study Completion:	7/2019
Final Report Submission:	1/2020

The following is a nonclinical PMR:

XXXX-1: Conduct a combination in vivo micronucleus and comet assay for (b) (4) The comet assay portion of the study should include assessment of both stomach and liver tissue and include doses of the drug substance that would be obtained at the maximum recommended daily dose of the drug product and result in adequate toxicity to ensure assay validity. (b) (4)

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	December 2014
Study Completion:	April 2015
Final Report Submission:	September 2015

The following is a clinical study to assess cardiovascular thromboembolic events:

XXXX-1: A postmarketing observational cohort study comparing Targiniq ER to other drugs approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The study's outcome is serious cardiovascular thromboembolic events; a concise case definition should be

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf

provided. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to Targiniq ER-exposed patients. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in serious cardiovascular thromboembolic risk above the comparator background rate, using a pre-specified statistical analysis method. For the Targiniq ER-exposed and comparator(s)-exposed patients, the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least six months of Targiniq ER exposure at the end of the study.

The following timetable proposes the schedule by which you will conduct this study:

Final protocol submission:	April 2015
Study completion:	April 2019
Final study report:	November 2019

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
07/23/2014